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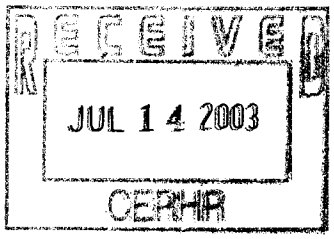
via US Mail and e-mail



Dr. Michael Shelby
CERHR
P.O. Box 12233
MD EC-32
Research Triangle Park, NC 27709

Re: Comments of the Propylene Oxide/Propylene Glycol Panel on the NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Propylene Glycol (NTP-CERHR-PG-03, May 2003)
68 Federal Register:26325 (May 15, 2003).

Dear Dr. Shelby:

The Propylene Oxide/Propylene Glycol Panel (PO/PG Panel) of the American Chemistry Council submits the attached comments in response to the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) *Expert panel Report on the Reproductive and Developmental Toxicity of Propylene Glycol* (Report) and the May 15, 2003 Federal Register Announcemnt. The member companies of the PO/PG Panel comprise the major domestic producers of propylene glycol in the United States.[1]

The PO/PG Panel commends the CERHR and expert panel participants for conducting an open and collegial review meeting, focused on the robust and voluminous scientific literature relevant to evaluation of the reproductive and developmental toxicity of the glycols. The PO/PG Panel agrees with the expert panel's conclusion that "*current estimated exposures to propylene glycol are of negligible concern for reproductive or developmental toxicity in humans*" (p. 76). While agreeing with the overall conclusions, the PO/PG Panel also notes that many of the deficiencies of the December 2002 draft Report, especially those in Chapter 2 ("General Toxicology and Biological Effects") remain unchanged in the May 2003 Report. As a result of the failure to heed the earlier comments, the expert panel's conclusions are not as strongly supported as the data demonstrate.

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[1] Members of the Propylene Oxide/Propylene Glycol Panel are The Dow Chemical Company, Huntsman Corporation, and Lyondell Chemical Company.

In lieu of reiterating previously submitted comments, the PO/PG Panel incorporates the comments of January 23, 2003 into these comments by reference, with a request that special attention be paid to the review by Dr. Mark Udden, a clinical hematologist at Baylor College of Medicine, of the failure to heed our earlier comments.

The comments included in the following submission expand on three significant deficiencies in the May 2003 Report that remain little changed from the December 2002 draft:

- Analysis of the data relating to wavy ribs and incomplete ossification of the vertebrae noted in the older FDA developmental toxicity study conducted in rats indicates that this common finding is not attributable to propylene glycol.
- Interpretation of information on the hematological effects of propylene glycol is inconsistent. Overall, evidence that propylene glycol adversely affects red blood cells in rats and humans is lacking.
- Evidence for the existence of potentially sensitive sub-populations is inconsistent, and the CERHR conclusion that such sub-populations exist is not justified.

Unfortunately, the CERHR does not contemplate further revision of the expert panel's Report. The PO/PG Panel requests therefore, that the deficiencies of the Report be addressed in the *NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Propylene Glycol* that will be prepared to complete the CERHR review process.

If you or your staff has any questions, please contact the PO/PG Panel Manager, Dr. Anne P. LeHuray at (703) 741-5630 or *anne_lehuray@americanchemistry.com.*

Sincerely yours,

Courtney M. Price
Vice President, CHEMSTAR

Enclosures

U.S. NATIONAL TOXICOLOGY PROGRAM (NTP)
CENTER FOR THE EVALUATION OF RISKS TO HUMAN REPRODUCTION (CERHR)

NTP-CERHR EXPERT PANEL REPORT ON THE REPRODUCTIVE AND DEVELOPMENTAL TOXICITY OF PROPYLENE GLYCOL

MAY 2003

NTP-CENTER-PG-03

COMMENTS OF THE PROPYLENE OXIDE/PROPYLENE GLYCOL PANEL OF THE AMERICAN CHEMISTRY COUNCIL

COMMENTS SUBMITTED: JULY 10, 2003

INTRODUCTION

The Propylene Oxide/Propylene Glycol Panel (PO/PG Panel) of the American Chemistry Council (ACC) submits these comments in response to the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) notice (68 Federal Register:26325, May 15, 2003) indicating that CERHR released the *Expert panel Report on the Reproductive and Developmental Toxicity of Propylene Glycol* (Report). As described in the Federal Register notice, the Report is intended to reflect "*the summaries and conclusions of the expert panel's evaluation of the scientific data for potential reproductive and/or developmental hazards associated with exposure to ... propylene glycol.*"

The expert panel met in February 2003 to review and evaluate reproductive and developmental toxicities of propylene glycol. In response to the draft Report released in preparation for the February meeting (67 Federal Register:236, Dec. 9, 2002), the PO/PG Panel submitted detailed comments on the draft Report on January 23, 2003. CERHR posted these comments on its web site (http://cerhr.niehs.nih.gov/news/egpg/pg_pubcomm.html) prior to the expert panel meeting.

The PO/PG Panel commends the CERHR and expert panel participants for conducting an open and collegial review meeting, focused on the robust and voluminous scientific literature relevant to evaluation of the reproductive and developmental toxicity of the glycols. The PO/PG Panel agrees with the expert panel's conclusion that "*current estimated exposures to propylene glycol are of negligible concern for reproductive or developmental toxicity in humans*" (p. 76). While agreeing with the overall conclusions, the PO/PG Panel also notes that many of the deficiencies of the December 2002 draft Report, especially those in Chapter 2 ("General Toxicology and Biological Effects") remain unchanged in the May 2003 Report. As a result of the failure to heed the earlier comments, the expert panel's conclusions are not as strongly supported as the data demonstrates.

In lieu of reiterating previously submitted comments, the PO/PG Panel incorporates the comments of January 23, 2003 into these comments by reference, with a request that special attention be paid to the review by Dr. Mark Udden, a clinical hematologist at Baylor College of Medicine, of the failure to heed our earlier comments.

This set of comments expands on three significant deficiencies in the May 2003 Report that remain little changed from the December 2002 draft:

- Analysis of the data relating to wavy ribs and incomplete ossification of the vertebrae noted in the older FDA developmental toxicity study conducted in rats indicates that this common finding is not attributable to propylene glycol.
- Interpretation of information on the hematological effects of propylene glycol is inconsistent. Overall, evidence that propylene glycol adversely affects red blood cells in rats and humans in lacking.
- Evidence for the existence of potentially sensitive sub-populations is inconsistent, and the CERHR conclusion that such sub-populations exist is not justified.

Unfortunately, the CERHR does not contemplate further revision of the expert panel's Report. The PO/PG requests therefore, that the deficiencies of the Report be addressed in the NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Propylene Glycol that will be prepared to complete the CERHR review process.

COMMENTS

1. Analysis of the data relating to wavy ribs and incomplete ossification of the vertebrae noted in the older FDA developmental toxicity study conducted in rats indicates that this common finding is not attributable to propylene glycol.

In two instances, the Report contains discussion of a purported effect of propylene glycol on wavy ribs and incomplete ossification of the vertebrae in the older FDA developmental toxicity study conducted in rats:

Page 61:

> With rats, higher numbers of wavy ribs and incomplete ossification of the vertebrae were observed at the same level as the positive control, suggesting a propylene glycol effect. The incidences of these defects did not appear to be dose-related.

Page 62:

> The appropriateness of the NOAEL level for rats (1,600 mg/kg bw/day) given in Table 3-11 depends on the importance attributed to the rib and vertebrae malformations observed.

Table 3-6 of the Report contains the data used to support these statements. Using the data in Table 3-6, the incidence and percentages for wavy ribs and incomplete ossification of the vertebrae have been calculated. The data is presented in the table below.

ENDPOINT - RATS	DOSE GROUP					
	CONTROL	POS. CONTROL	16 MG/KG	74.3 MG/KG	340 MG/KG	1600 MG/KG
Wavy ribs						
pup incidence	1/173	46/137	23/179	27/169	11/167	15/180
litter incidence	1/22	16/20	9/23	11/22	5/20	8/24
% pup	0.60%	34%	13%	16%	7%	8%
% litter	5%	80%	39%	50%	25%	33%
Vertebrae – incomplete ossification						
pup incidence	0/0	101/137	1/179	13/169	3/167	18/180
litter incidence	0/0	19/20	1/23	7/22	3/20	9/24
% pup	0%	74%	0.50%	8%	2%	10%
% litter	0%	95%	4%	32%	15%	38%

As demonstrated in the table, the data do not support the statement that "*With rats, higher numbers of wavy ribs and incomplete ossification of the vertebrae were observed at the same level as the positive control....*" Clearly the positive control values (80%, 95%) are more than twice as high as those reported even in the 1,600 mg/kg high dose group (33%, 38%).

One may question whether there was an effect in these endpoints based upon comparison with the negative control ("Control") group. Given the differences in the strains of rats used in the 1973 FDA study and those currently available, it would be inappropriate to conduct a quantitative comparison of the incidence of wavy ribs and incomplete ossification of the vertebrae from historical databases currently available in testing laboratories. However, as a qualitative comparison, it is important to note that historically, wavy ribs and incomplete ossification of the vertebrae are very common findings in developmental toxicity studies conducted with rats. The most striking finding, evident in the data in the table above, is the unusually low incidence of these lesions in the negative control population.

Additional support for discounting the significance of these findings is the lack of any dose-response relationships for these endpoints. For example, in the case of the wavy ribs, the lowest dose level tested (16 mg/kg; 100-fold lower than the high dose group) had a higher incidence that the highest dose level tested (1,600 mg/kg).

2. Interpretation of information on the hematological effects of propylene glycol is inconsistent. Overall, evidence that propylene glycol adversely affects red blood cells in rats and humans in lacking.

The PO/PG Panel previously (January 23, 2003) submitted extensive comments to CERHR on the interpretation of hematological data for propylene glycol presented in the December 2002 draft Report. The previous submission included an expert evaluation of publications cited in the draft Report, prepared by Dr. Mark Udden, a clinical hematologist at Baylor College of Medicine. The May 2003 Report contains little evidence that Dr. Udden's review has been taken into account. Rather than repeat these comments (which remain valid and are presented again to CERHR for consideration), the focus here is instead on the inconsistencies in the Report text noted in the paragraphs that follow.

Section 2.2.2.4, page 38, fourth paragraph

> Christopher et al. (*91*)[1] provide an excellent study that establishes a plausible mechanism for propylene-induced hemolysis and the Bauer et al. (89) study provides important confirmatory evidence for the impairment of hematopoiesis by propylene glycol. Thus the hemolysis potential of high doses of propylene glycol, which is a plausible effect, is firmly established in two species (cat and dog) and reasonably well substantiated in other species including man.

This statement is an over-generalization of the available scientific data, and ignores the several established metabolic and physiological factors that predispose red blood cells from the cat to propylene glycol-induced toxicity. These are well known to the expert panel, because they are discussed at length by Christopher *et al.* (91) and also summarized by Dr. Udden. It is therefore difficult to understand why the expert panel Report appears to conclude that results obtained in the cat are indicative of a potential for propylene glycol to cause adverse hematological effects in humans: overall scientific evidence to support this is lacking. The work of Christopher, Bauer and co-workers focused on the susceptibility of the cat to propylene glycol-induced Heinz body formation with no mention of 'hemolysis' (which appears to be the

[1] Numbers in parentheses refer to the reference numbers of citations in the Report.

main end-point of interest to the expert panel). There also does not appear to be any evidence from either study for any inhibition of hematopoiesis (cited by the expert panel Report as a toxic response to propylene glycol). The PO/PG Panel strongly recommends that CERHR reconsider the basis for these conclusions, which are at variance with the published data.

Indeed, the only evidence presented by the expert panel in support of the "hemolytic capability" of propylene glycol in humans is a 65-year old *in vitro* study by Braun and Cartland (79). The expert panel is referred to Dr. Udden's report which includes several more up-to-date references and which also serves to put these *in vitro* findings into context: the findings are an osmotic, not a toxiciological, phenomenon seen at propylene glycol concentrations of 30% or greater. This contrasts with human *in vivo* data cited elsewhere by the expert panel (*e.g.*, Chicella *et al.*; (66)), which indicates that the maximum concentration of propylene glycol in serum from patients undergoing intravenous (IV) drug therapy is 763±660 mg/l (*i.e.*, approximately 0.08-0.14%), which is several hundred fold lower than that shown to cause hemoloysis *in vitro*. This data suggest that red blood cell hemolysis in patients exposed to propylene glycol by IV infusion is unlikely to be an issue.

With regard to the expert panel's view that the information from Saini *et al.* (90) "*confirms that the haemotopoietic system is also a target of propylene glycol in rats*," the PO/PG Panel again questions the scientific reliability of hematological data obtained from animals subjected to four retro-orbital bleeds within two days with no concurrent control group. Certainly there was a clear effect on some parameters that were measured, but with no controls it cannot be determined if this was due to propylene glycol or day-to-day experimental variability.

Overall, the expert panel's conclusions on the potential hematotoxicity of propylene glycol in humans is unsupported.

3. Evidence for the existence of potentially sensitive sub-populations is inconsistent, and the CERHR conclusion that such sub-populations exist is not justified.

The PO/PG Panel previously submitted (January 23, 2003) extensive comments on the expert panel's view that individuals with compromised liver or kidney function, burn patients or premature infants may be "at increased risk for developing propylene glycol toxicity." There is little evidence that the previous comments have been taken into account in revising the Report, apart from inclusion of some moderating words (*i.e.*, "overdosage of premature infants"; "complex clinical case studies") in the introductory paragraph of Section 2.5 (page 44). Rather than repeat the previously submitted comments (which remain valid) the focus here instead is on inconsistencies in the report text described in paragraphs that follow.

Section 2.5, paragraph 1, line 6 (page 44)

> Patients with impaired liver or kidney function would be at increased risk for developing propylene glycol toxicity (*48*).

This is a logical statement given the importance of hepatic metabolism and renal excretion in overall clearance of propylene glycol from the body. It also seems self-evident that the toxicokinetics and toxicodynamics of propylene glycol will be altered in individuals with pre-existing liver or kidney disease or who develop hepatic or renal insufficiency as a result of clinical treatment. Against this background, interpretation of case reports of lactic acid acidosis,

increased osmolality and other clinical sequelae requires careful objective assessment: while propylene glycol may have been present in the circulation, there is only anecdotal evidence that propylene glycol was responsible for the effects reported in these individuals. This should be made clear in the Report, and the individual references cited by the expert panel should be assessed to determine if the references are scientifically reliable.

Section 2.5.1, page 44, final sentence

> Serum concentrations of propylene glycol received through IV medications have been shown to correlate with serum lactate concentrations in patients with normal renal and hepatic function (*51*).

The expert panel cites Kelner and Bailey (51), who reported serum propylene glycol and lactate concentrations in 5 subjects (two middle aged adults, three infants aged 4 months or younger) with 'normal' renal and liver function and who concluded that "propylene glycol administration may be an important cause of lactic acid acidosis" as support for this statement. In reaching this conclusion, Kelner and Bailey developed a regression model for relating serum concentrations of propylene glycol and lactate in their patients *i.e.,*

$$Y = 0.034X + 2.97$$

where Y is the lactate concentration in serum (mEq/l) at a propylene glycol concentration of X (mg/l). This suggests there is a clear (numerically positive) relationship between propylene glycol and lactate levels in serum.

However, other data cited in the Report, namely the publication by Chicella *et al.* (66; not present in the earlier version of the Report) lead to a very different conclusion. In Chicella *et al.* (66), no correlation was observed between serum propylene glycol and lactate in 11 patients (aged 1-15 months) receiving IV medication containing propylene glycol. Since Chicella *et al.* was a prospective study designed specifically to address issues of interest to the CERHR, it is unclear why its findings have been overlooked in favor of other less reliable data.

As part of their investigation, Chicella *et al.* recorded serum propylene glycol concentrations in their subjects at various time points leading to mean values of 85, 519 and 763 mg/l at (roughly) the start, middle and end of treatment. These are consistent with measured serum propylene glycol concentrations reported by Kelner and Bailey (roughly in a range of 50-400 mg/l). Based on the data and modeling of Kelner and Bailey, equivalent mean serum lactate values of 5.9, 21 and 29 mEq/l would be predicted for the Chicella subjects. In fact Chicella *et al.* reported very modest measured lactate values of 1.9, 1.7 and 1.7 mmol/l, respectively (consistent with their conclusion that no lactic acid acidemia was present in these patients).

The expert panel should consider the data of Chicella *et al.*, rather than those of Kelner and Bailey, to support the conclusions of section 2.5: that propylene glycol is a low concern for lactic acid acidemia.

Section 2.5.2, first line, page 45

> The decreased size of premature infants, and an increased serum half-life for propylene glycol in premature infants (*35, 36*), predispose them to a greater probability of toxic effects from over administration of propylene glycol.

Studies reported by Fligner *et al.* (35), Glasgow *et al.* (36) and Huggon *et al.* (70) are used to support this and related statements present in this section of the Report. As discussed in

the PO/PG Panel's January 23, 2003 submission, patients included in the cited case reports were already suffering from pre-exisiting clinical conditions that likely had a fundamental impact on the disposition of propylene glycol in the body, or they were administered powerful, potentially toxic pharmaceutical treatments as part of their therapy, or a combination of the two. This presumably explains in part the expert panel's observation (page 13, line 7) that data from Fligner *et al.* and Glasgow *et al.* reflect "circumstances that preclude confident extrapolation to a healthy general population." Huggon *et al.* also add a warning that impaired renal failure may have contributed to the increased osmolality recorded in their study. Given the unreliability of this information, the expert panel should re-evaluate whether these studies support the conclusion that premature infants are at greater risk of propylene glycol toxicity.

It is also clear from data presented in Chicella *et al.* (66) that no adverse responses were reported in slightly older infants (age 1-15 months) following IV drug therapy that resulted in a mean serum propylene glycol concentration as high as 763 mg/ml. Therefore, the basis of the expert panel's decision (Section 2.5.2, paragraph 3, final sentence) to "caution" that it may be necessary to monitor lactic acidosis and hyperosmolality in pediatric patients given IV infusions containing propylene glycol is unknown.

Given the considerable uncertainties in these studies (detailed in the PO/PG Panel's January 23, 2003 submission) the conclusion of the May 2003 Report, that the studies provide evidence of a sub-population with an enhanced sensitivity to propylene glycol related toxicity is questionable.

Section 2.5.2, first paragraph, last line (page 45):

> .....propylene glycol.....was associated with cardiopulmonary arrest in one case (*70*).

This statement, citing Huggon *et al.* (70) is factually incorrect: circulatory problems were present in this individual before any exposure to propylene glycol. There is no mention of propylene glycol-induced "cardiopulmonary arrest" in the publication.